

BMJ Open Risk of bladder cancer in patients with diabetes: a retrospective cohort study

Maria E Goossens,¹ Maurice P Zeegers,² Marloes T Bazelier,³ Marie L De Bruin,³ Frank Buntinx,^{1,4} Frank de Vries^{3,5,6,7}

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ABSTRACT

Objective: The objective of this study was to examine the association between diabetes, and both urinary bladder cancer (UBC) risk and mortality.

Methods: We conducted a retrospective cohort study using data from the UK Clinical Practice Research Datalink (CPRD) linked to the Office of National Statistics (ONS). Patients diagnosed with diabetes mellitus type 1 or 2, or using antidiabetic drugs (ADDs), were compared to matched non-diabetic controls. Cox proportional hazards models were used to estimate the risk and mortality of UBC. We adjusted for age, sex, smoking status and body mass index.

Results: The cohort included 329 168 patients using ADD, and 307 315 controls with 1295 and 1071 patients, respectively, diagnosed as having UBC during follow-up. The adjusted HRs of UBC were 0.77 (95% CI 0.57 to 1.05) and 1.04 (95% CI 0.96 to 1.14) for type 1 and 2 diabetes, respectively. These results were similar if we restricted our analysis to an inception cohort. We noticed a small increased risk during the first year after diagnosis (HR=1.26 (95% CI 1.05 to 1.52)), which could be explained by detection bias. There was no influence of the severity of diabetes as measured by the glycated haemoglobin. Mortality of UBC was not increased for patients with either type 1 (HR=0.95 (95% CI 0.39 to 2.34)) or type 2 diabetes (HR=1.16 (95% CI 0.91 to 1.46)).

Conclusions: Neither the risk of UBC nor the mortality from UBC was increased in patients with type 1 and patients with type 2 diabetes in the CPRD data.

BACKGROUND

The global 2013 estimate of diabetes mellitus prevalence among adults (aged 20–79 years) was 8.3%, affecting 382 million adults in the world and 6.6% in the UK.¹ Between 2010 and 2030, the number of adults with diabetes in developing countries is expected to increase by 69%, and by 20% in developed countries.^{2,3} In 2012, more than 400 000 cases of urinary bladder cancer (UBC) occurred worldwide, making it the seventh most common type of cancer.⁴ It is more frequent in men than in women, and age is now widely accepted as the greatest single

Strengths and limitations of this study

- The Clinical Practice Research Datalink (CPRD) is a large population-based cohort representative of the total UK population.
- Detailed longitudinal information on drug prescription is available within the CPRD, and 95% and 80% of patients with type 1 and 2 diabetes, respectively, had received a formal diabetes diagnosis.
- Smoking status was available for all patients in our analysis.
- Detailed information about the cause of death is available for 44% of the patients by linking the patients to the Office of National Statistics (ONS) data.
- The effect of different antidiabetic drug medications is not considered in our analyses and this is a major limitation.

risk factor for developing UBC. Cigarette smoking and specific occupational exposures, such as carcinogenic dyes for painters and some genetic polymorphisms, are the other main known causes of UBC.⁵ Previous meta-analyses from cohort and case-control studies have shown an increased risk of UBC associated with type 2 diabetes with relative risks (RR) ranging from 1.11 (95% CI 1.00 to 1.23) to 1.32 (95% CI 1.18 to 1.49).^{6–9} There is also evidence for a positive association between type 2 diabetes and mortality from UBC (RR=1.33 (95% CI 1.14 to 1.55)).⁷ However, misclassification of type 1 and 2 diabetes was not excluded in these studies, because diagnostic codes were lacking and details about the diabetic history (duration, metabolic control) were not considered.

Two studies on type 1 diabetes reported an increased overall cancer incidence by 20%, while the mechanisms remain unclear.^{10,11} The observed number of bladder cancer cases in these studies is very small, ranging from 4 to 27 cases.^{10–12} The objective of this study was to examine the association between diabetes mellitus, and both UBC risk and mortality, taking into account diabetes



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For numbered affiliations see end of article.

Correspondence to

Frank de Vries;
f.devries@uu.nl

duration, metabolic control as expressed by glycated haemoglobin (HbA1c) and type of diabetes.

METHODS

Data sources

We conducted a retrospective cohort study using data from the UK Clinical Practice Research Datalink (CPRD) (January 1987–October 2013) linked to the Office of National Statistics (ONS) (January 1998–January 2012). The CPRD comprises prospectively collected computerised medical records of over 10 million patients under the care of more than 600 general practitioners (GPs) in the UK. The Read classification is used to enter medical diagnoses and procedures, and prescriptions are recorded based on the UK *Prescription Pricing Authority Dictionary*.

The recorded information on diagnoses and drug use was validated, and proved to be of high quality.¹³ The ONS provided data for the cause(s) of death and the exact date of death as recorded on death certificates by a registered medical practitioner attending to the patient during their last period.

Study population

All patients with at least one prescription of antidiabetic drugs (ADDs) (oral antidiabetic drugs (NIADs) and/or insulin) and aged above 18 years during the period of valid CPRD data collection were included. Each ADD user was matched to one control patient by year of birth, sex and practice. Controls could have any disease as long as they were non-diabetic patients at baseline and during follow-up. The date of the first ADD prescription defined the index date and controls were assigned the same index date as their matched ADD user. All participants with missing data for smoking status, a history of any cancer prior to the index date, except non-melanoma skin cancer, or a diagnosis of gestational diabetes or secondary diabetes ever during follow-up were excluded. All control patients who used diabetes treatment or had ever been diagnosed with type 1 or 2 diabetes ever during follow-up were excluded. All ADD users with diagnoses of type 1 and 2 diabetes were excluded as well, as were patients aged 30 years and older without a diagnosis of diabetes, who used insulin only at baseline. All study participants were followed up from the index date to either the end of data collection, the date of transfer of the patient out of the practice area, or the patient's death.

Exposure

Patients with type 1 diabetes were defined as those patients with a formal diagnosis of type 1 diabetes (as recorded in CPRD) or younger than 30 years and using insulin only at index date. Patients with type 2 diabetes were all patients with a formal diagnosis of type 2 diabetes (as recorded in CPRD) or using an oral ADD at index date. The total period of follow-up for each patient (patients with diabetes and unexposed controls)

was divided into fixed time periods of 90 days. Age was determined at the start of each interval. The classification of type 1 and 2 diabetes, as well as sex, smoking status and body mass index (BMI), was determined at baseline. Diabetes duration was assessed in a time-dependent manner by estimating the time since the date of the first ADD prescription (the index date). Diabetes control was assessed in a time-dependent manner using the most recent HbA1c record before the start of each time interval and within the previous year.

Outcomes

The primary outcome was UBC, as defined by Read codes, and was assessed in the complete CPRD study population (January 1987–October 2013). The secondary outcome was bladder cancer-related mortality as recorded on death certificates (International Classification of Diseases (ICD-10) categories C65, C67) and was assessed in the population eligible for linkage between CPRD and ONS data (44% of the participants). The period of follow-up was restricted to the time that ONS data were available (January 1998–January 2012).

Risk factors

The major covariates of interest included age, sex, smoking status and BMI. Smoking status was characterised at baseline as current, former or lifelong non-smoker.

Statistical analysis

Analyses were conducted using Cox proportional hazards models with various subanalyses. As time scale we used time since first ADD use. We tested the proportional hazard assumption by comparing patients with diabetes to non-diabetes controls. The assumption was not violated. The first analysis compared the risk of UBC in ADD users with that in control patients to yield an estimate of the RR (as a HR) of UBC associated with ADD use. The calculations were adjusted for age, sex, smoking status and BMI. Results were stratified to type 1 and type 2 diabetes. A sensitivity analysis was performed excluding women with polycystic ovarian syndrome (PCOS). In a secondary analysis, risks were estimated for an inception cohort of ADD users using a 1-year lead-in time. The risk of UBC for patients with incident type 2 diabetic was further stratified by disease duration, sex and HbA1c. The risk of UBC mortality in ADD users compared with that of controls was assessed by Cox models as well and results were stratified by type of diabetes. All data management and statistical analyses were conducted using SAS V.9.1/9.2 software.

This study was approved by the Medicines and Healthcare products Authorities' Independent Scientific Advisory Committee, protocol number 13_050R.

RESULTS

After exclusion of all patients with a diagnosis of gestational diabetes (1983 and 154 for ADD users and

controls, respectively), or secondary diabetes (485 and 70 for ADD users and controls, respectively), or cancer prior to index date (34 955 and 34 384 for ADD users and controls, respectively) or missing data for smoking status during follow-up (13 416 and 27 558 for ADD users and controls, respectively), the study population consisted of 329 168 patients with diabetes of whom 30 823 (9.4%) and 298 345 (90.6%) had type 1 and 2 diabetes, respectively, and 307 315 controls. Patients diagnosed with type 1 and 2 diabetes at baseline (7614) and patients without diagnosis, using insulin only at baseline and 30 years or older (10 178), were not included in our analysis.

Table 1 shows baseline characteristics. The mean age at index date was 58 years. Forty-six per cent of the patients with diabetes had a BMI of 30 or above in contrast with 30% of the control participants.

During nearly 6 years of follow-up, 1071 patients of the control group and 1295 of the ADD users were diagnosed with bladder cancer. Patients with type 1 diabetes

had no significantly lower risk of UBC (HR=0.77 (95% CI 0.57 to 1.05)) than patients with type 2 diabetes (HR=1.04 (95% CI 0.96 to 1.14)) based on a Wald test ($p=0.054$). The results for incident ADD users were similar (table 2).

For patients with incident type 2 diabetes, we noticed an increased risk of UBC (HR=1.26 (95% CI 1.05 to 1.52)) during the first year after the first ADD prescription, compared to controls, which disappeared in subsequent years (table 3). Sixty per cent of the bladder cancers developed during the first 5 years after diabetes onset. There was no difference in UBC risk between male and female patients with type 2 diabetes (HR=1.11 (95% CI 0.98 to 1.25) and 1.01 (95% CI 0.79 to 1.29), respectively). In patients with type 2 diabetes, there was no influence of HbA1c as an indicator of diabetes severity on UBC risk (table 4). UBC-related mortality was neither increased in patients with type 1 diabetes (HR=0.79 (95% CI 0.32 to 1.94)) nor in patients with type 2 diabetes, compared to controls (HR=1.05 (95% CI 0.83 to 1.33)) (table 5).

Table 1 Baseline characteristics of antidiabetic drug (ADD) users and non-diabetic controls

Characteristics	ADD users N=329 168	(Per cent)	Controls 307 315	(Per cent)
Follow-up time (years; mean)	5.91		5.66	
Sex				
Female	152 683	(46.4)	148 791	(48.4)
Male	176 485	(53.6)	158 524	(51.6)
Age at index date (years; mean, median)	58.6 (60.0)		58.2 (60.0)	
18–29	19 716	(6.0)	19 184	(6.2)
30–39	26 236	(8.0)	28 065	(9.1)
40–49	43 659	(13.3)	41 539	(13.5)
50–59	68 564	(20.8)	62 400	(20.3)
60–69	80 562	(24.5)	71 975	(23.4)
70–79	62 064	(18.9)	56 632	(18.4)
80+	28 367	(8.6)	27 520	(9.0)
Smoking status				
Never smoker	168 832	(51.3)	166 190	(54.1)
Current smoker	66 903	(20.3)	70 765	(23.0)
Former smoker	93 433	(28.4)	70 360	(22.9)
Body mass index (kg/m ²)				
<20.0	6 587	(2.0)	16 769	(5.5)
20.0–24.9	54 212	(16.5)	96 636	(31.4)
25.0–29.9	105 547	(32.1)	103 315	(33.6)
≥30.0	150 152	(45.6)	55 827	(18.2)
Unknown	12 670	(3.8)	34 768	(11.3)
ADD users				
Formal diabetes diagnosis				
Type 1	28 964	(8.8)		
Type 2	239 021	(72.6)		
No diabetes diagnosis				
Insulin only at index date and <30 years	1859	(0.6)		
Others	59 324	(18.0)		
Patients with diabetes				
Type 1 diabetes*	30 823	(9.4)		
Type 2 diabetes†	298 345	(90.6)		

*Defined as either formal diagnosis of type 1 diabetes or insulin only at index date and younger than 30 years.

†Defined as either formal diagnosis of type 2 diabetes or ADD use at index date.

Table 2 Risk of bladder cancer in antidiabetic drug (ADD) users compared with controls, by type of diabetes and in incident ADD users

Exposure category	ADD users (N=329 168) versus controls (N=307 315)			Incident ADD users (N=179 598) versus controls (N=233 505)		
	Bladder cancer N (%)	Age-sex adj HR (95% CI)	Fully adj HR* (95% CI)	Bladder cancer N (%)	Age-sex adj HR (95% CI)	Fully adj HR* (95% CI)
Controls	1071 (0.3)	1	1	732 (0.3)	1	1
ADD users	1295 (0.4)	1.09 (1.00 to 1.18)	1.03 (0.95 to 1.12)	746 (0.4)	1.15 (1.04 to 1.27)	1.08 (0.97 to 1.20)
Type 1 diabetes†	44 (0.0)	0.76 (0.56 to 1.02)§	0.77 (0.57 to 1.05)	5 (0.0)	0.65 (0.27 to 1.58)	0.65 (0.27 to 1.57)
Type 2 diabetes‡	1251 (0.4)	1.10 (1.02 to 1.20)	1.04 (0.96 to 1.14)	741 (0.4)	1.15 (1.04 to 1.28)	1.09 (0.97 to 1.21)

*Incident=all index patients are included after 1 year lead-in time without antidiabetic drug (ADD) prescription; fully adjusted for age, sex, smoking and body mass index.

†Defined as either formal diagnosis of type 1 diabetes or insulin only at index date and younger than 30 years.

‡Defined as either formal diagnosis of type 2 diabetes or ADD use at index date.

§Significant difference between type 1 diabetes mellitus and type 2 diabetes mellitus, based on Wald test.

DISCUSSION

We could not detect a significantly increased risk of UBC nor of increased mortality due to UBC in patients with type 1 and 2 diabetes compared to controls even if we reduced our cohort to incident ADD users. However, we noticed an increased risk of UBC in patients with type 2 diabetes during the first year after diagnosis. Diabetes control, as expressed by HbA1c, had no influence on the UBC risk in patients with type 2 diabetes.

Previous meta-analyses reported an increased risk.⁶⁻⁹ Even when these meta-analyses⁶⁻⁸ were restricted to studies that adjusted for smoking, there was still an increased RR ranging from 1.32 (95% CI 1.18 to 1.49) to 1.48 (95% CI 1.25 to 1.77), comparable to our RR for type 2 diabetes. On the other hand, in several studies, diabetes ascertainment was based on self-reporting.⁸ Those studies had an RR of 1.34 (95% CI 1.11 to 1.62).

The increased risk of UBC in patients with diabetes decreased and significance disappeared when diabetes was asserted by other methods (RR=1.11 (95% CI 0.95 to 1.31)). Furthermore, not all studies distinguished between diabetes type 1 and 2. Most of the studies excluded type 1 diabetes as a diagnosis of diabetes before 30 years of age.⁷⁻⁸ Subgroup analysis of studies restricted to Europe did not show an increased risk of UBC in patients with type 2 diabetes.⁶⁻⁸ Hence, our results are in line with those of European studies.¹²⁻¹⁴⁻²¹ It is not clear why there is a difference between European studies and those of other regions.

We did not find an increased risk of bladder cancer in diabetes type 1, which is in line with the results found in Sweden¹⁰⁻¹¹ and in the UK.¹²

An increased risk of UBC during the first year after diabetes diagnosis was found in several other

Table 3 Risk of bladder cancer in incident patients with type 2 diabetes mellitus compared with controls, by duration of disease and sex

Exposure category	Type 2 diabetes (N=175 083) versus controls (N=233 505)		
	Bladder cancer N (%)	Age-sex adj HR (95% CI)	Fully adj HR* (95% CI)
Controls	732 (0.3)	1	1
Type 2 diabetes	741 (0.4)	1.15 (1.04 to 1.28)	1.09 (0.97 to 1.21)
Duration of disease (years)†			
<1	149 (0.1)	1.34 (1.12 to 1.61)	1.26 (1.05 to 1.52)
1- $<$ 2	95 (0.1)	1.17 (0.95 to 1.45)	1.10 (0.88 to 1.37)
2- $<$ 5	201 (0.1)	1.02 (0.87 to 1.19)	0.95 (0.81 to 1.12)
5- $<$ 10	224 (0.1)	1.22 (1.05 to 1.41)	1.14 (0.98 to 1.33)
10- $<$ 15	67 (0.0)	1.19 (0.93 to 1.54)	1.14 (0.88 to 1.47)
\geq 15	5 (0.0)	0.43 (0.18 to 1.04)	0.42 (0.18 to 1.02)
Sex			
Male‡	604 (0.3)	1.19 (1.06 to 1.33)	1.11 (0.98 to 1.25)
Female§	137 (0.1)	1.03 (0.82 to 1.29)	1.01 (0.79 to 1.29)

*Incident=all index patients are included after 1 year lead-in time without antidiabetic drug (ADD) prescription; fully adjusted for age, sex, smoking and body mass index.

†As measured from first prescription.

‡Male patients with type 2 diabetes versus male controls.

§Female patients with type 2 diabetes versus female controls.

Table 4 Risk of urinary bladder cancer in patients with type 2 diabetes mellitus by HbA1c level at most recent measurement

Exposure category	Patients with type 2 diabetes (N=298 345)		
	Bladder cancer N (%)	Age-sex adj HR (95% CI)	Fully adjusted HR* (95% CI)
Type 2 diabetes	1251 (0.4)		
HbA1c level†			
HbA1c <6%	57 (0.0)	1	1
6≤HbA1c <7.0%	278 (0.1)	1.18 (0.89–1.57)	1.19 (0.90–1.58)
7≤HbA1c <8.0%	248 (0.1)	1.16 (0.87–1.55)	1.18 (0.89–1.58)
8≤HbA1c <9.0%	110 (0.0)	1.09 (0.79–1.50)	1.10 (0.80–1.52)
HbA1c ≥9.0%	106 (0.0)	1.17 (0.85–1.62)	1.17 (0.85–1.62)
Missing	452 (0.2)	0.91 (0.68–1.20)	0.92 (0.69–1.21)

*Fully adjusted for age, sex, smoking and body mass index.

†6%=42 mmol/mol, 7%=53 mmol/mol, 8%=64 mmol/mol, 9%=75 mmol/mol.

HbA1c, glycated haemoglobin.

studies.^{20 22–24} Likewise, for colorectal, lung, breast, liver, cervical, endometrial, ovarian, pancreatic and prostate cancers, a significantly increased risk was found within the months following diabetes onset.^{10 25 26} This most likely indicates the presence of a detection bias, in the sense that the diagnosis of diabetes leads to increased medical attention, and thus to earlier detection of any present but undiagnosed cancer. This phenomenon has also been observed immediately after the diagnosis of prostate cancer. The incidence of UBC was 18 times higher in patients with prostate cancer due to diagnostic bias.^{27 28} On the other hand, in contrast with some other studies, we could not confirm the hypothesis that fewer physician visits in the year before diabetes diagnosis increases the risk of bladder cancer diagnosis in contrast with some other studies.^{24 26} Apart from the increased risk of UBC during the first year of diabetes diagnosis, possibly due to detection bias, we did not find an association between diabetes duration and developing bladder cancer. Seeing that nearly 50% of the patients had a follow-up of more than 5 years and only 40% of the bladder cancers were diagnosed after these 5 years, while only 10% was diagnosed after 10 years, we can conclude that having diabetes for more than 5 years did not alter the risk of UBC.

Our finding of no association between HbA1c and cancer risk is consistent with the results of a recent meta-analysis of major randomised controlled trials.²⁹

The strength of this study was that the CPRD is a large population-based cohort, representative of the total UK population. Type 2 diabetes accounts for 85% to 95% of all diabetes in high-income countries.¹ In the UK, 10% of the people with diabetes have type 1,³⁰ which was confirmed in our analysis (9.4%). We had detailed longitudinal information on drug prescription, and 95% and 80% of the patients with type 1 and 2 diabetes, respectively, had received a formal diabetes diagnosis. Patients with type 1 and 2 diabetes at baseline, and patients without diagnosis, using insulin only at baseline and 30 years or older, were excluded from our analysis. Consulting rates for diabetes in the CPRD have been compared with equivalent data from the fourth National Morbidity Survey in General Practice, confirming the validity of the morbidity data in the CPRD.³¹ Furthermore, since 2004, GPs have been stimulated to provide ‘quality care’ by the Quality and Outcomes Framework (QOF). The UK has a National Service Framework for Diabetes (NSF).³² Guidelines to be followed by the GPs are outlined in the guideline for type 1³³ and 2 diabetes³⁴ of the National Institute of Health and Care Excellence (NICE). For diagnosis, the NICE guideline refers to the International Diabetes Federation (IDF) Diabetes Atlas.¹ Diagnosis of diabetes is directly linked with prescription of ADD whereas Impaired Glucose Tolerance (IGT) is referred to as people whose blood glucose levels are high but not as high as those in people with diabetes. Our

Table 5 Risk of urinary bladder cancer (UBC) mortality in antidiabetic drug (ADD) users compared with controls, by type of diabetes mellitus

Exposure category	ADD user (N=143 566) versus controls (N=114 994)		
	Bladder cancer mortality N (%)	Age-sex adjusted HR (95% CI)	Fully adjusted HR* (95% CI)
Controls	145 (0.1)	1	1
ADD users	179 (0.1)	1.04 (0.83 to 1.29)	1.04 (0.83 to 1.31)
Type 1 diabetes	5 (0.0)	0.73 (0.30 to 1.79)	0.79 (0.32 to 1.94)
Type 2 diabetes	174 (0.1)	1.05 (0.84 to 1.31)	1.05 (0.83 to 1.33)

*Fully adjusted for age, sex, smoking and body mass index.

cohort was restricted to those patients receiving ADD. Furthermore, we had HbA1c values for 1251 of the 1295 patients with bladder cancer. So, 96% of the patients have additional proof of being diabetic.

Metformin can also be used to treat obesity or PCOS. We have no means to test the possible effect of metformin prescribed for obesity, although the clinical impression exists that such treatments tend to be relatively short. In our cohort, 12 841 women were diagnosed with PCOS. None of them developed UBC. A sensitivity analysis, excluding those PCOS women, showed exactly the same HRs. Additionally, we have information on the smoking status of all patients who were included in our analysis, which is essential given that smoking is one of the major risk factors for bladder cancer.⁵ The link with the ONS data allowed us to have detailed information about the cause of death for 44% of patients.

The fact that the effect of different antidiabetic drug medications was not considered in our analyses is a major limitation. We are aware of the fact that metformin can have a protective effect on cancer^{3 35} and that pioglitazone could be associated with an increased risk of bladder cancer.^{36–40} This was, however, beyond the scope of this study.

With this study, and against the background of all previous research, the likelihood of a clinically relevant association between diabetes and UBC risk has become very limited. The influence of antidiabetic treatment on bladder cancer risk, however, is still contradictable and requires further study in the future.

CONCLUSION

Neither the risk of UBC nor the mortality from UBC was observed to be increased in patients with type 1 or type 2 diabetes in the CPRD data. Our results are in line with those of previous European studies.

Author affiliations

¹Department of General Practice, KU Leuven, Leuven, Belgium

²Department of Complex Genetics, University of Maastricht, NUTRIM School of Nutrition, Translational Research in Metabolism, Maastricht, The Netherlands

³Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht Institute of Pharmaceutical Sciences, The Netherlands

⁴Department of General Practice, University of Maastricht, CAPHRI, School for Primary Care and Public Health, Maastricht, The Netherlands

⁵Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre, Maastricht, The Netherlands

⁶Research Institute CAPHRI, University of Maastricht, The Netherlands

⁷MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK

Contributors MEG wrote the manuscript and researched data. MTB performed the statistical analysis and reviewed the manuscript. FB and MPZ reviewed/edited the manuscript. FdV and MLDB provided the data and reviewed/edited the manuscript.

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Data sharing statement CPRD data are available under license with the Medicines and Healthcare products Regulatory Agency (MHRA) in London, UK. The datasets that have been used for this project have been licensed by the MHRA. Access to datasets that have been used for this study are available for audit purposes only, conditional on permission by the MHRA.

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Maria E Goossens, Maurice P Zeegers, Marloes T Bazelier, Marie L De Bruin, Frank Buntinx and Frank de Vries

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